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(74) continued overleaf

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WO 99/35146 A1 WO 99/35132 A1

(58) Field of Search
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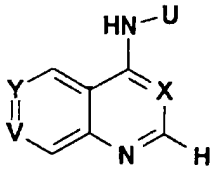
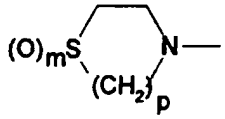
(54) Abstract Title
Heteroaromatic protein tyrosine kinase inhibitors

(57) Substituted heteroaromatic compounds of formula (I)



(I)

wherein X is N or CH;
Y is CR^1 and V is N;
or Y is N and V is CR^1;
or Y is CR^1 and V is CR^2;
or Y is CR^2 and V is CR^1;
R^1 represents a group Q-(CH_2)q-Ar, wherein Q is a group of formula



wherein m is 1 or 2; p is 1 or 2; q is 1, 2, 3 or 4; and Ar is selected from phenyl, furan, thiophene, pyrrole and thiazole, each of which may optionally be substituted by one or two halo, C_{1-4} alkyl or C_{1-4} alkoxy groups; R^2 is selected from the group comprising hydrogen, halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4}alkylamino and di[C_{1-4}alkyl]amino;

(57) continued overleaf

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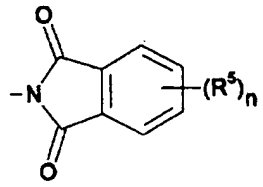
United Kingdom

(57) cont

U represents a phenyl, pyridyl, 3H-imidazolyl, indolyl, isoindolyl, indolinyl, isoindolinyl, 1H-indazolyl, 2,3-dihydro-1H-indazolyl, 1H-benzimidazolyl, 2,3-dihydro-1H-benzimidazolyl or 1H-benzotriazolyl group, substituted by an R^3 group and optionally substituted by at least one independently selected R^4 group;
R^3 is selected from a group comprising benzyl, halo-, dihalo- and trihalobenzyl, benzoyl, pyridylmethyl, pyridylmethoxy, phenoxy, benzyloxy, halo-, dihalo- and trihalobenzyloxy and benzenesulphonyl;
or R^3 represents a group of formula



wherein each R^5 is independently selected from halogen, C_{1-4}alkyl and C_{1-4}alkoxy; and n is 0 to 3;
each R^4 is independently hydroxy, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di[C_{1-4} alkyl]amino, C_{1-4} alkylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, C_{1-4} alkylcarbonyl, carboxy, carbamoyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkanoylamino, N-(C_{1-4} alkyl)carbamoyl, N,N-di(C_{1-4} alkyl)carbamoyl, cyano, nitro and trifluoromethyl,
and salts and solvates thereof, are protein tyrosine kinase inhibitors.

HETEROCYCLIC COMPOUNDS

The present invention relates to a series of substituted heteroaromatic compounds, methods for their preparation, pharmaceutical compositions containing them and their use in medicine. In particular, the invention relates to quinoline, quinazoline, pyridopyridine and pyridopyrimidine derivatives which exhibit protein tyrosine kinase inhibition.

Protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth and differentiation (A.F. Wilks, Progress in Growth Factor Research, 1990, 2, 97-111; S.A. Courtneidge, Dev. Supp.l, 1993, 57-64; J.A. Cooper, Semin. Cell Biol., 1994, 5(6), 377-387; R.F. Paulson, Semin. Immunol., 1995, 7(4), 267-277; A.C. Chan, Curr. Opin. Immunol., 1996, 8(3), 394-401). Protein tyrosine kinases can be broadly classified as receptor (e.g. EGFr, c-erbB-2, c-met, tie-2, PDGFr, FGFr) or non-receptor (e.g. c-src, lck, zap70) kinases. Inappropriate or uncontrolled activation of many of these kinase, i.e. aberrant protein tyrosine kinase activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth.

Aberrant activity of protein tyrosine kinases, such as c-erbB-2, c-src, c-met, EGFr and PDGFr have been implicated in human malignancies. Elevated EGFr activity has, for example, been implicated in non-small cell lung, bladder and head and neck cancers, and increased c-erbB-2 activity in breast, ovarian, gastric and pancreatic cancers. Inhibition of protein tyrosine kinases should therefore provide a treatment for tumours such as those outlined above.

Aberrant protein tyrosine kinase activity has also been implicated in a variety of other disorders: psoriasis, (Dvir et al, J.Cell.Biol; 1991, 113, 857-865), fibrosis, atherosclerosis, restenosis, (Buchdunger et al, Proc.Natl.Acad.Sci. USA; 1991, 92, 2258-2262), auto-immune disease, allergy, asthma, transplantation rejection (Klausner and Samelson, Cell; 1991, 64, 875-878), inflammation (Berkois, Blood; 1992, 79(9), 2446-2454), thrombosis (Salari et al, FEBS; 1990, 263(1), 104-108) and nervous system diseases (Ohmichi et al, Biochemistry, 1992, 31, 4034-4039). Inhibitors of the specific protein tyrosine kinas s involved in these diseases eg PDGF-R in restenosis and EGF-R in psoriasis, should lead to novel therapies for

such disorders. P56lck and zap 70 are indicated in disease conditions in which T cells are hyperactive e.g. rheumatoid arthritis, autoimmune disease, allergy, asthma and graft rejection. The process of angiogenesis has been associated with a number of disease states (e.g. tumourogenesis, psoriasis, rheumatoid arthritis) and this has been shown to be controlled through the action of a number of receptor tyrosine kinases (L.K. Shawver, DDT, 1997, 2(2), 50-63).

It is therefore a general object of the present invention to provide compounds suitable for the treatment of disorders mediated by protein tyrosine kinase activity, and in particular treatment of the above mentioned disorders.

In addition to the treatment of tumours, the present invention envisages that other disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition, including preferential inhibition, of the appropriate protein tyrosine kinase activity.

Broad spectrum inhibition of protein tyrosine kinase may not always provide optimal treatment of, for example tumours, and could in certain cases even be detrimental to subjects since protein tyrosine kinases provide an essential role in the normal regulation of cell growth.

It is another object of the present invention to provide compounds which preferentially inhibit protein tyrosine kinases, such as EGFr, c-erbB-2, c-erbB-4, c-met, tie-2, PDGFr, c-src, lck, Zap70, and fyn. There is also perceived to be a benefit in the preferential inhibition involving small groups of protein tyrosine kinases, for example groups including two or more of c-erbB-2, c-erbB-4, EGF-R, lck and zap70.

A further object of the present invention is to provide compounds useful in the treatment of protein tyrosine kinase related diseases which minimise undesirable side-effects in the recipient.

The present invention relates to heterocyclic compounds which may be used to treat disorders mediated by protein tyrosine kinases and in particular have anti-cancer properties. More particularly, the compounds of the present invention are potent inhibitors of protein tyrosine kinases such as such as EGFr, c-erbB-2, c-erbB-4, c-

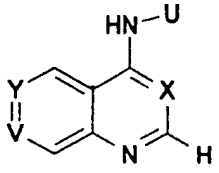
met, tie-2, PDGFr, c-src, lck, Zap70, and fyn, thereby allowing clinical management of particular diseased tissues.

The present invention envisages, in particular, the treatment of human malignancies, for example breast, non-small cell lung, ovary, stomach, and pancreatic tumours, especially those driven by EGF-R or erbB-2, using the compounds of the present invention. For example, the invention includes compounds which are highly active against the c-erbB-2 protein tyrosine kinase often in preference to the EGF receptor kinase hence allowing treatment of c-erbB-2 driven tumours. However, the invention also includes compounds which are highly active against both c-erbB-2 and EGF-R receptor kinases hence allowing treatment of a broader range of tumours.

The present invention also includes compounds which are active against lck and/or zap70 receptor kinases; these may also be active against c-erbB-2 and/or EGF-R receptor kinases. The compounds may be selective towards lck and/or zap70 in comparison to c-erbB-2 and/or EGF-R.

More particularly, the present invention envisages that disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition of the appropriate protein tyrosine kinase activity in a relatively selective manner, thereby minimising potential side effects.

Accordingly, the present invention provides a compound of formula (I)



(I)

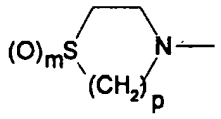
or a salt or solvate thereof;

wherein X is N or CH;

Y is CR^1 and V is N;
or Y is N and V is CR^1;
or Y is CR^1 and V is CR^2;

or Y is CR^2 and V is CR^1;

R^1 represents a group Q-(CH_2)q-Ar, wherein Q is a group of formula



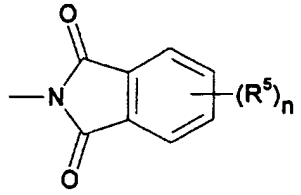
wherein m is 1 or 2; p is 1 or 2; q is 1, 2, 3 or 4; and Ar is selected from phenyl, furan, thiophene, pyrrole and thiazole, each of which may optionally be substituted by one or two halo, C_{1-4} alkyl or C_{1-4} alkoxy groups;

R^2 is selected from the group comprising hydrogen, halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino and di[C_{1-4} alkyl]amino;

U represents a phenyl, pyridyl, 3H-imidazolyl, indolyl, isoindolyl, indolinyl, isoindolinyl, 1H-indazolyl, 2,3-dihydro-1H-indazolyl, 1H-benzimidazolyl, 2,3-dihydro-1H-benzimidazolyl or 1H-benzotriazolyl group, substituted by an R^3 group and optionally substituted by at least one independently selected R^4 group;

R^3 is selected from a group comprising benzyl, halo-, dihalo- and trihalobenzyl, benzoyl, pyridylmethyl, pyridylmethoxy, phenoxy, benzyloxy, halo-, dihalo- and trihalobenzyloxy and benzenesulphonyl;

or R^3 represents a group of formula

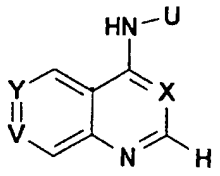


wherein each R^5 is independently selected from halogen, C_{1-4} alkyl and C_{1-4} alkoxy; and n is 0 to 3;

each R^4 is independently hydroxy, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di[C_{1-4} alkyl]amino, C_{1-4} alkylthio, C_{1-4} alkylsulphinyl,

C_{1-4} alkylsulphonyl, C_{1-4} alkylcarbonyl, carboxy, carbamoyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkanoylamino, N-(C_{1-4} alkyl)carbamoyl, N,N-di(C_{1-4} alkyl)carbamoyl, cyano, nitro and trifluoromethyl.

In another aspect the present invention provides a compound of formula (I)

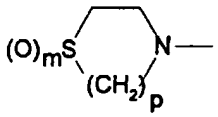


(I)

or a salt of solvate thereof;

wherein X, Y, V, R^2, U, R^3 and R^4 are as defined above;

and wherein R^1 represents a group Q-(CH_2)q-Ar, wherein q and Ar are as defined above; and Q is a group of formula



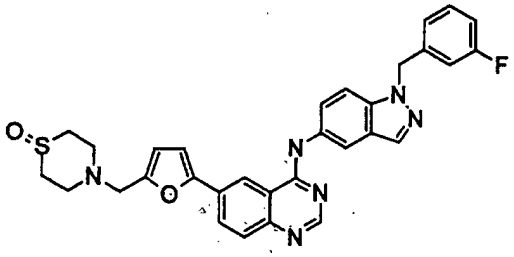
in which m is 0 and p is 1.

Solvates of the compounds of formula (I) are also included within the scope of the present invention.

The definitions for X, Y and V thus give rise to a number of possible basic ring systems for the compounds of formula (I). In particular the compounds may be contain the following basic ring systems:

thiomorpholine-S-oxide (1 to 3 equiv.). δ ^{1}H NMR (DMSO) 10.02 (s, 1 H), 8.80 (s, 1 H), 8.56 (s, 1 H), 8.17 (d, 1 H), 8.04 (d, 1 H), 7.82 (d, 1 H), 7.77 (m, 1 H), 7.50 (m, 1 H), 7.37-7.29 (m, 3 H), 7.21 (m, 1 H), 7.13 (d, 1 H), 6.57 (d, 1 H), 5.29 (d, 1 H), 3.74 (s, 2 H), 3.01-2.89 (m, 4 H), 2.80-2.75 (m, 4 H); m/z (M+1) 576.

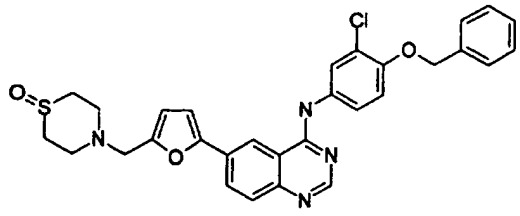
Example 14



(3-Fluorobenzyl-1H-indazol-5-yl)-(6-(5-(1-oxo-1.λ.4-thiomorpholin-4-ylmethyl)-furan-2-yl)quinazolin-4-yl)amine

Prepared according to alternative Procedure D from 4-{[5-(4-{[1-(3-fluorobenzyl)-1H-indazol-5-yl]amino}-6-quinazolinyl)-2-furan-carboxaldehyde (1 equiv.) and thiomorpholine-S-oxide (1 to 3 equiv.). δ ^{1}H NMR (DMSO) 10.09 (s, 1 H), 8.81 (s, 1 H), 8.51 (s, 1 H), 8.25-8.16 (m, 3 H), 7.83-7.70 (m, 3 H), 7.40 (m, 1 H), 7.10 (m, 4 H), 6.58 (d, 1 H), 5.73 (s, 2 H), 3.74 (s, 2 H), 2.99-2.90 (m ,4 H), 2.81-2.76 (m, 4 H); m/z (M+1) 576.

Example 15

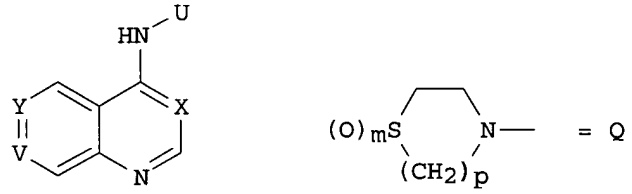


(4-Benzyloxy-3-chlorophenyl)-(6-(5-(1-oxo-1.λ.4-thiomorpholin-4-ylmethyl)-furan-2-yl)quinazolin-4-yl)amine

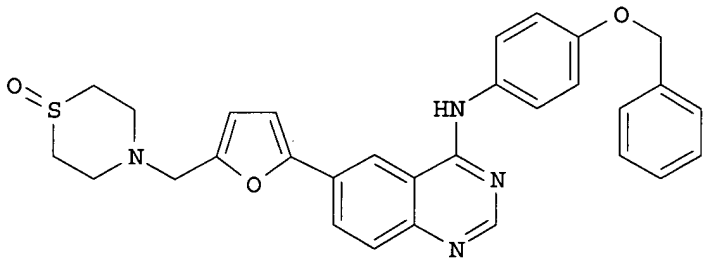
L10 ANSWER 8 OF 72 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:854415 CAPLUS
DOCUMENT NUMBER: 133:362769
TITLE: Preparation of 6-(thiomorpholinomethylfuranyl)-4-quinazolinamines as protein tyrosine kinase inhibitors
INVENTOR(S): Carter, Malcolm Clive; Cockerill, George Stuart; Guntrip, Stephen Barry; Lackey, Karen Elizabeth; Smith, Kathryn Jane
PATENT ASSIGNEE(S): Glaxo Group Ltd., UK
SOURCE: Brit. UK Pat. Appl., 151 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2345486	A1	20000712	GB 1999-29973	19991217

PRIORITY APPLN. INFO.: GB 1999-518 A 19990111
GB 1999-15510 A 19990703
OTHER SOURCE(S): MARPAT 133:362769
GI



I



II

AB The title compds. (I) [wherein X = N or CH; V and Y = independently CR1, CR2, or N; and V .noteq. Y; R1 = Q(CH2)qAr; m = 1 or 2; p = 1 or 2; q = 1-4; Ar = (un)substituted Ph, furanyl, thiophenyl, pyrrolyl, or thiazolyl; R2 = H, halo, OH, alkyl(amino) alkoxy, or dialkylamino; U = (un)substituted Ph, pyridyl, (benz)imidazolyl, (iso)indolyl, (iso)indolinyl, indazolyl, or benzotriazolyl] were prepd. as protein tyrosine kinase inhibitors for the treatment of cancer and other disorders mediated by aberrant protein tyrosine kinase activity. For example, II.bul.2HCl was formed in a multi-step sequence involving (1) reaction of 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)furan with (4-benzyloxyphenyl)(6-bromoquinazolin-4-yl)amine using Pd(PPh3)2Cl2 in dioxane, (2) conversion of the cyclic acetal to the aldehyde with HCl in THF, (3) addn. of

thiomorpholine-S-oxide in CH2Cl2 and conversion to the HCl salt. I inhibited EGFR and c-erbB-2 tyrosine kinase with IC50 < 0.10 .mu.M and suppressed cell proliferation against a range of tumor cell lines.

IT **307328-34-3P**, 1-(3-Fluorobenzyl-1H-indazol-5-yl)[6-[5-((1-oxothiomorpholin-4-yl)methyl)furan-2-yl]quinazolin-4-yl]amine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of thiomorpholinomethylfuranyl quinazolinamine and pyrido[3,4-d]pyrimidinamine anticancer agents by amination of (haloheterocyclyl)furancarboxaldehydes with anilines followed by addn. of thiomorpholine (oxides))

RN 307328-34-3 CAPLUS

CN 4-Quinazolinamine, N-[3-[(3-fluorophenyl)methyl]-1H-indazol-5-yl]-6-[5-[(1-oxido-4-thiomorpholinyl)methyl]-2-furanyl]- (9CI) (CA INDEX NAME)